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(16952 CON1-CIP3)

PATENT

REMARKS

Upon entry of this response, claims 1-5 will be pending in this application. Amended claims 1 and 5 are clearly supported by the specification at, for example, page 3, lines 5-25. Claims 6-28 have been canceled as they are directed to a non-elected subject matter, and Applicant reserves the right to file the subject matter of these claims in one or more applications at a later time.

As a preliminary matter, it is important to understand that the recited pure neurotoxin of the claimed invention is clearly different from the neurotoxin of Tse. For example, the recited pure neurotoxin of the claimed invention is about **150 kDa**, comprising a short polypeptide chain of about **50 kDa** and a long polypeptide chain of about **100 kDa**.

On the other hand, the neurotoxin of Tse is about **140 kDa**, comprising a first polypeptide of **99 kDa** and a second polypeptide of about **55 kDa** (See Tse et al., Eur. J. Biochem., 1982, 122:493-500, 497, first column, (hereinafter "the Tse reference").

As will be presented in detail below, the claimed invention is not obvious over the combination of cited references because there is no motivation to combine the cited references. Moreover, even if the cited references were combined, the combination of the cited references does not result in the claimed invention, because for example, the neurotoxin of Tse is clearly not the pure neurotoxin recited in the claimed invention.

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1. Priority Under 35 U.S.C. 119 (e)

Applicant is entitled to the priority date of application serial number 08/173,996, filed December 28, 1993 (hereinafter "the parent application"), because the specification of the parent application fully describes the effective amount of the botulinum toxin free of a complex protein (i.e., pure botulinum toxin) to treat strabismus. For example, page 1, line 23, of the specification of the parent application discloses that botulinum toxins can be used to treat strabismus (also, see page 2, lines 4-7); page 3, lines 5-14, discloses a neurotoxic component of a botulinum toxin having a molecular weight of about 150 kDa (i.e., pure botulinum toxin) which can be useful in the method of the present invention; page 4, lines 9-12, discloses that conventional techniques are known for culturing and purifying a botulinum toxin; page 8, lines 22-31, discloses that effective doses of the pure botulinum toxin may be less than 1000 units, for example between about 80-460 units.

Further, with respect to effective doses of the pure botulinum toxin, the specification of the parent application discloses that the dose administered depends upon the severity of the condition, e.g., number of muscle groups requiring treatment. Thus, one of ordinary skill would know the appropriate dose to administer. Moreover, the courts have recognized that determining an effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be strabismus in the present case) is well within the ordinary skill in the art. *In re Bundy*, 209 U.S.P.Q. 48 (C.C.P.A. 1981). As such, the specification of the parent application fully describes the claimed invention.

Accordingly, Applicant respectfully requests that the Office grants the priority filing date of December 28, 1993 to the present application.

Moreover, as the claimed invention has a priority date of December 28, 1993, the following cited references cannot be relied upon by the Office: Han (2001) and Aoki (1999).

II. Non-Obviousness

Overview

The claimed invention is believed to be patentable over the combination of cited reference because there is **no motivation** to combine the references for at least the following reasons:

(1) human muscles (claimed invention) are different from rat muscles (Tse);

(2) at the time of the priority date of the claimed invention (December 28, 1993), there was a general belief that purified botulinum toxin is clinically ineffective; and

(3) the teachings of the Balkan/Han references are to provide methods for clinical treatment of strabismus in humans. On the other hand, the teachings of the Tse reference are to provide improved vaccines and probes.

Assuming *arguendo* that there is motivation to combine the references, **the combination of the references does not result the claimed invention**. For example, the recited pure neurotoxin of the claimed invention is about **150 kDa**, comprising a short polypeptide chain of about **50 kDa** and a long polypeptide chain of about **100 kDa**. The Office Action relied on Tse to for the disclosure of a pure neurotoxin. However, the pure neurotoxin of Tse is about **140 kDa**, comprising a first polypeptide of **99 kDa** and a second polypeptide of about **55 kDa** (See Tse et al., Eur. J. Biochem., 1982, 122:493-500, 497, first column, (hereinafter "the Tse reference"). Since the neurotoxin of Tse is not the same as that of the claimed invention, even if Tse is combined with Balkan and Han, the combination does not result in the claimed invention.

Detailed Analysis For Non-Obviousness

Claims 1-5 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the abstract of Balkan et al., Annals of Ophthalmology, 1991 Sep, 23(9):326-333 or the abstract of Han et al., Journal of Pediatric Ophthalmology and Strabismus, 2001 Mar-

Apr, 38(2): 68-71 (hereinafter "the Balkan/Han references") in view of the Tse reference and the Aoki reference.

As discussed above, the claimed invention is entitled to a priority date of December 28, 1993. Accordingly, the Han, and Aoki references cannot be relied upon by the Office.

Assuming *arguendo* that the Han, and Aoki references may be relied upon by the Office, the claimed invention is still inventive over the cited combination of references.

The Office Action's states that the claims are obvious because, as detailed by the October 18, 2005 Office Action, although the Balkan/Han references only teach the use of complexed botulinum toxin to treat strabismus, it would have been obvious to one of ordinary skill to use purified botulinum toxin to treat strabismus

> because pure neurotoxin has similar activity in the paralysis of muscles as complexed neurotoxin and has similar activity against spontaneous release of acetylcholine [as disclosed by the Tse reference] and because that botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection [as disclosed by the Aoki reference].

The October 18, 2005 Office Action, at pages 3-4.

A. Patent Office's Burden to Show Prima Facie Case of Obviousness

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Office to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from applicant's disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd.

Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done.

(citations omitted; emphasis added). Significantly, the Office Action identifies no "motivating force" that would "impel" a person of ordinary skill to combine the teachings of the Balkan/Han references in view of the Tse reference and Aoki reference to arrive at the present invention.

B. Non-Obviousness Over The Balkan/Han and Tse References

There is no "motivating force" that would "impel" a person of ordinary skill to combine the teachings of the Balkan/Han references and the Tse reference at least for the following reasons:

1. Human Muscles Are Different From Rat Muscles

The Balkan/Han references report on the injection of complexed botulinum toxin into a human spasmodic medial rectus muscle and lateral rectus muscle for treating strabismus. On the other hand, the Tse reference reports on the injection of botulinum toxin into a non-spasmodic rat hind leg muscle. Clearly, **the Balkan/Han references relate to human muscles, while the Tse reference relate to rat muscles**; and it is well documented that the effects of botulinum toxin on rat's muscles cannot be extrapolated to that of human's. For example, Jankovic et al. asserts that

> Unfortunately, given the species-specificity of the various toxin types, rodent studies must be considered inconclusive with respect to predicting the relative clinical potency of the various types of BTX.

Jankovic et al., Therapy with Botulinum Toxin, 1994 Marcel Dekker, Inc., page 76, last paragraph (Exhibit 1, previously submitted on December 22, 2005). Thus, one of ordinary skill would not combine the Balkan/Han references with the Tse reference because the information reported in the latter relating to the effects of botulinum toxin on mouse muscles cannot be applied to human muscles.

Note also that Jankovic et al. was published much later (1994) than Tse (1982). Moreover, Jankovic et al. was published in the year that was much closer in time to the priority filing date (1993) of the claimed invention. Accordingly, the disclosure of Jankovic et al. is more current than Tse, and is more relevant and more reflective of the state of the art for when the present application was filed.

2. General Belief That Purified Botulinum Toxin Is Clinically Ineffective

At the time of the filing of the present application, one of ordinary skill would **not consider the teachings of the Tse reference regarding the use of purified botulinum toxin to be relevant to clinical treatment,** such as the treatment of strabismus in humans. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. Specifically, Schantz et al. states:

> Most recent information concerning the structure and pharmacology of botulinum toxin has been obtained with purified neurotoxins, but **it is unlikely that these will be used in clinical settings**. The toxin complexes are much more stable than neurotoxin and can be diluted and formulated with retention of toxicity. Pure neurotoxins can be kept for several weeks to months in solution in the cold but are inactivated on dilution, formulation, and drying.

Schantz et al., Microbiological Reviews, Mar 1992, p. 80-99, 89, second column, emphasis added (Exhibit 2, previously submitted on December 22, 2005). Since it was believed at the time of filing the present application that purified botulinum toxin would not be effective for clinical use, one of ordinary skill would not be impelled to combine the teachings of the Tse reference (use of purified botulinum toxin in non-clinical settings, i.e., rat experiments) with the teachings of the Balkan/Han references (use of complexed botulinum toxin in clinical setting for treating strabismus in humans).

It is important to note that Schantz et al. makes the statement quoted above even though Schantz et al. was fully aware that purified botulinum toxin had been tested in rats. For example, the Schantz reference cited the Tse reference on the second column on page 83, and Sellin et al. (Acta Physiol Scan, 983; 119:127-33, hereinafter "the Sellin reference", Exhibit 3 which was previously submitted on December 22, 2005) on page 89, which reported on experiments similar to that of the Tse reference, i.e., injection of purified botulinum toxin type B into the lower hind limb of a rat to produce paralysis. Nevertheless, the Schantz reference asserted that the use of purified botulinum toxin would be clinically ineffective on page 89.

Also, note that Schantz et al. was published much later (1992) than Tse (1982). Moreover, Schantz was published in the year that was much closer in time to the priority filing date (1993) of the claimed invention. Accordingly, the disclosure of Schantz et al. is more current than Tse, and is more reflective of the state of the art for when the present application was filed.

3. The Teachings Of The Balkan/Han References Have A Different Purpose Than That Of The Tse Reference

The teachings of the Balkan/Han references are to provide methods for clinical treatment of strabismus in humans. On the other hand, the teachings of the Tse reference are to provide improved vaccines and probes. Specifically, the Tse reference states:

> It is, therefore, believed that purified neurotoxin could provide a superior and novel vaccine ... Finally, as the pure neurotoxin is known to inhibit specifically neurotransmitter release at peripheral ... and central synapses ..., it could be an invaluable probe for nerve membrane component(s) concerned with the release processes...

The Tse reference, at page 493, second column. The use botulinum toxin as a drug for treating strabismus in humans is very different from the use of botulinum toxin as an antigen or a probe, and the practice of the two methods may be entirely incompatible with each other. For example, one of the goals for using botulinum toxin in treating strabismus is to be able to administer the botulinum toxin in a dose/regimen as to not induce antibody production against the toxin, since the induction of antibody against the botulinum toxin would render the toxin less effective. On the other hand, the primary goal of using botulinum toxin as an antigen is to induce antibody production against the toxin. Since the teachings of the Balkan/Han references are for a different purpose than that of the Tse reference, one of ordinary skill would not be impelled to combine these references.

The Office states that the Tse reference discloses at page 494 that an injection of a "neurotoxin free of Haemagglutinin, when injected into the hind leg muscle of a rat, produced local paralysis within 24 hours..." Applicant cannot find this particular disclosure, and respectfully requests that the Office point outs the column and paragraph on page 494 where this disclosure is found.

Even if the Tse reference does disclose that the administration of a pure neurotoxin can produce a local paralysis in a rat, Applicant respectfully directs the Office to the arguments made above that data from rat muscles cannot be extrapolated to human muscles.

4. The Combination of Cited References Does Not Result in the Claimed Invention

Assuming *arguendo* that there is motivation to combine the references, **the combination of the references does not result the claimed invention.** For example, the recited pure neurotoxin of the claimed invention is about **150 kDa**, comprising a short polypeptide chain of about **50 kDa** and a long polypeptide chain of about **100 kDa**. The Office Action relied on Tse to for the disclosure of a pure neurotoxin. However, the pure neurotoxin of Tse is not the same as that of the claimed invention. That is, the pure neurotoxin of Tse is about **140 kDa**, comprising a first polypeptide of **99 kDa** and a second polypeptide of about **55 kDa** (See Tse et al., Eur. J. Biochem., 1982, 122:493-500, 497, first column, (hereinafter "the Tse reference"). Since the neurotoxin of Tse is not the same as that of the claimed invention, even if Tse is combined with Balkan and Han, the combination does not result in the claimed invention. Thus, the claimed invention is patentable over the combination of the cited references.

C. Non-Obviousness Over The Balkan/Han References And The Aoki Reference

The Office Action on alleges that one of ordinary skill would be motivated to modify the teachings of the Balkan/Han reference to using a purified botulinum toxin because

> Aoki et al. teaches that botulinum toxin complexes (MW greater than 150 kda) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection of botulinum toxin complex [as compared to botulinum toxin of 150, i.e., purified botulinum toxin]...

The Office Action at page 3. It appears that the Office Action is assuming that the a high rate of diffusion of the botulinum toxin is desirable for the treatment of strabismus. To the contrary, in strabismus conditions, very specific muscles are spasmodic, and only those specific muscles need to be treated with botulinum toxin. It is not desirable that the administered botulinum toxin diffuse to adjacent muscles that need to remain untreated. Thus, it appears that the Aoki reference is even teaching away from the present invention, by teaching that purified botulinum toxin would diffuse more quickly to adjacent

muscles, and thus purified botulinum toxins should not be used to treat strabismus. In deed, it is the Applicant who surprisingly discovered that purified botulinum toxin may be effectively used for treating strabismus.

The Office Action may assert that a neurotoxin injected into one eye muscle can never diffuse to another eye muscle, stating "Since the [eye] muscles are separated, the improperly functioning eye muscle can be treated without the toxin diffusing to the other muscles." Respectfully, this assumption is incorrect. For example, the inferior oblique eye muscle overlaps the inferior rectus eye muscle, and the point of overlap may be the point of where the neurotoxin can diffuse/cross over from one muscle to the other.

III. Double Patenting

U.S. Patent Application No. 10/443,593

Claims 1-5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-11 of co-pending U.S. Patent Application No. 10/443,593 (hereinafter "the 593 application").

Applicant hereby submits a terminal disclaimer under 37 C.F.R. 1.1321(c) with respect to the 593 application for claims 18 and 21-29 of the present application. Thus, the obviousness-type double patenting rejection should be withdrawn.

U.S. Patent No. 6,841,156

Claims 1-5 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,841,156 (hereinafter "the 156 patent") in view of Tse and Aoki et al.

Applicant hereby submits a terminal disclaimer under 37 C.F.R. 1.1321(c) with respect to the 156 patent for claims 1-5 of the present application. Thus, the obviousness-type double patenting rejection should be withdrawn.

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Applicant asserts that the **terminal disclaimers are submitted for the sole purpose of administrative efficiency**, and Applicant respectfully disagrees that the pending claims are obvious over the 593 application or the 156 patent. (The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991), MPEP §804.02 II).

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

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